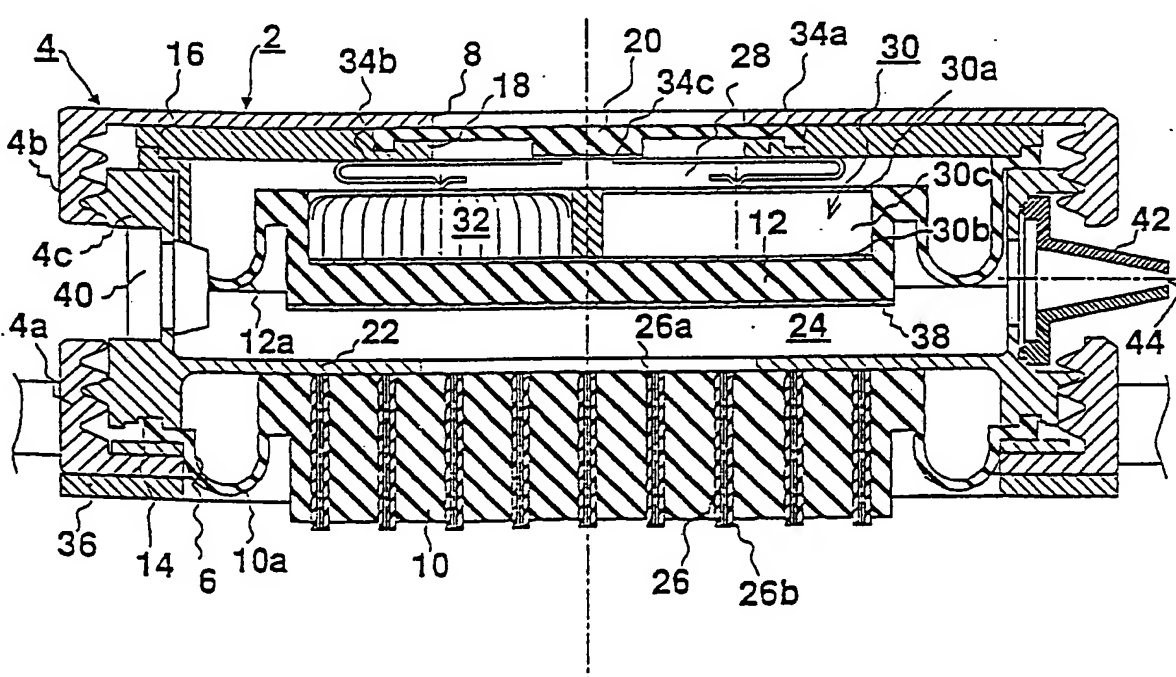




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>5</sup> :  A61N 1/30</p>	<p>A1</p>	<p>(11) International Publication Number: WO 93/17754  (43) International Publication Date: 16 September 1993 (16.09.93)</p>
<p>(21) International Application Number: PCT/EP93/00562 (22) International Filing Date: 11 March 1993 (11.03.93)  (30) Priority data: 07/850,595 13 March 1992 (13.03.92) US 07/981,652 25 November 1992 (25.11.92) US  (71) Applicant: ELAN MEDICAL TECHNOLOGIES LIMITED [IE/IE]; Monksland Industrial Estate, Athlone, County Westmeath (IE).  (72) Inventors: GROSS, Joseph ; 73 160 Moshav Mazor (IL). ZUCKER, Shlomo ; 1 Hapardes Street, 40 297 Mihmor-et (IL).  (74) Agents: MODIANO, Guido et al.; Modiano, Josif, Pisanty &amp; Staub, Baaderstr. 3, D-8000 München 5 (DE).</p>		<p>(81) Designated States: AU, CA, JP, KR, NZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: DRUG DELIVERY DEVICES</p>  <p>(57) Abstract</p> <p>A drug delivery device includes a liquid reservoir (24) for a liquid drug to be delivered, and a drug delivery body which includes a plurality of tubular elements (26) or hollow needles extending through the body, each having an inlet end communicating with the liquid reservoir, and an outlet end projecting from the body and engageable with the subject's skin to conduct the liquid drug directly to the subject's skin.</p>		

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DRUG DELIVERY DEVICES

The present invention relates to transdermal or interdermal drug delivery devices for delivering a liquid drug to a subject via the subject's skin. The invention is particularly useful with respect to the drug delivery device described in our Patent No.5,156,591, and is therefore described below with respect to that device, but it will be appreciated that the invention could advantageously be used in other types of drug delivery devices.

Our Patent No.5,156,591 describes a transdermal drug delivery device which delivers a drug to the subject by means of an electrically-induced mass transfer phenomenon called iontophoresis. This process for drug delivery has recently become of great interest, and many such transdermal delivery devices have been described in the patent literature, including US Patents 4,164,226, 4,640,689, 4,708,716, 4,752,285, 4,693,711, 5,057,072, US Statutory Invention Registration H516, and European Patent Application Publication 0299631. Other methods of electrically-aided or electrically-controlled transdermal drug delivery devices are described in US Patent 4,886,513, as well as in our prior US Patents 5,062,834 and 5,090,963.

According to the present invention, there is provided a drug delivery device for delivering a liquid drug to a subject via the subject's skin, comprising: a housing; a liquid reservoir in the housing for a liquid drug to be delivered; and a drug delivery body carried by the housing and having one side communicating with one side of the liquid reservoir, and the opposite side exposed to engage the skin of the subject to receive the drug; characterized in that the drug delivery body includes a plurality of stiff tubular elements extending through the body, each having an inlet end communicating with the liquid reservoir, and an outlet end at said opposite side of the drug delivery body to conduct the liquid drug directly to said opposite side.

The plurality of stiff tubular elements may be in the form of hollow needles having inner diameters of less than 1 mm and projecting at least 0.1 mm from the face of the drug delivery body. Preferably, the drug delivery body includes at least fifty of such stiff tubular elements or hollow needles. Their tips may be cut at a bias to pierce the outer layer of dead cells on the skin and thereby to enhance the penetration of the drug.

In the use of the device, the plurality of tubular elements are pressed firmly against the subject's skin, and thereby provide a better delivery of the drug to the subject's skin, as compared to the use of microporous or matrix-type drug delivery bodies as in the prior art. The device also permits better control of the drug delivery rate. When the delivery is effected by iontophoresis, the better delivery of the drug enables lower electrical currents to be used, thereby decreasing the danger of burning or irritating the subject's skin.

Fig. 1 is a top plan view illustrating one form of transdermal drug delivery device constructed in accordance with the present invention;

Fig. 2 is a bottom plan view of the device of Fig. 1;

Fig. 3 is an enlarged sectional view along line III-III of Fig. 2;

Figs. 4, 5 and 6 are views similar to that of Fig. 3 but illustrating three further forms of drug delivery devices constructed in accordance with the present invention;

and Figs. 7a-7e illustrate various tip constructions of the stiff tubular elements extending through the drug delivery body.

The transdermal drug delivery device illustrated in Figs. 1-3 of the drawings, and generally designated 2, is applied by a band 3 to the arm or leg of the subject, with one side of the device (that side illustrated in Fig. 2) firmly pressed against the subject's skin. The device 2 is

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a self-contained unit which includes a reservoir for the liquid drug to be delivered, as well as electrodes for delivering the drug by means of the iontophoresis electrically-induced mass transfer phenomenon. Device 2 further includes an electrolytic cell which, together with the iontophoresis electrodes, controls the rate of feed of the drug to the subject, and an electrical battery for powering both the iontophoresis electrodes and the electrolytic cell.

10           The internal structure of the transdermal drug delivery device 2 is more particularly illustrated in Fig. 3. It includes a housing 4 of plastic material and of circular configuration. Housing 4 is made of an inner section 4a, an outer section 4b, and an intermediate section 15 4c threadedly joining sections 4a and 4b together. The inner section 4a is formed with a large circular opening 6, and the outer section 4b is formed with a smaller circular opening 8.

          An inner membrane 10 is clamped between housing sections 4a and 4c, and an outer membrane 12 is clamped between housing sections 4b and 4c. Both membranes 10 and 12 are of elastomeric material and include annular flexible sections 10a, 12a, to make them displaceable in response to pressure. Membrane 10 is aligned with the center opening 6 in housing section 4a and is clamped between that housing section and the intermediate section 4c via a ring 14. Membrane 12 is clamped between the intermediate housing section 4c and the outer housing section 4b via a disc 16 having a central opening 18 in alignment with opening 8 in the outer housing section 4b. A third membrane 20 is clamped between disc 16 and the outer housing section 4b to close opening 8.

          Membrane 10 is displaceable outwardly of housing 4 by its annular flexible section 10a, but is restrained against inward displacement by a rigid annular disc 22 integrally formed with the intermediate housing section 4c. Membrane 12, however, is displaceable in both directions by

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its annular flexible section 12a. Membrane 20 is similarly displaceable in both directions with respect to openings 8 and 18 in housing section 4b and disc 16, respectively.

5 The two membranes 10, 12 define, between them, a chamber 24 serving as a liquid reservoir for the liquid drug to be delivered by the device 2. Membrane 10 serves as a drug delivery body through which the drug is delivered. For this purpose, membrane 10 includes a plurality of tubular elements 26 extending through it, with each tubular element  
10 having an inlet end 26a communicating with the liquid reservoir 24, and an outlet end 26b engageable with the subject's skin.

A second chamber 28 is defined between membrane 12 and disc 16 and its membrane 20. Chamber 28 serves as a  
15 pressure-control chamber for controlling the pressure applied to the drug chamber 24 for controlling the rate of feed of the liquid drug via tubular elements 26 through the drug delivery membrane 10. For this purpose, chamber 28 includes an electrolytic cell, generally designated 30,  
20 comprising a pair of electrodes 30a, 30b and an electrolyte 30c which generates a gas in accordance with the current passing through it. Such electrolytic cells are well known and are capable of generating a gas (e.g., oxygen and/or hydrogen) when an electrical current is applied.

25 Electrolytic cell 30 is located in one side of a cavity formed in membrane 12. The other side of the cavity serves as a compartment for a button-type battery 32 powering the electrolytic cell 30. Electrode 30a of the electrolytic cell is connected to one side of the battery  
30 via spring clips 34a and 34b electrically connected together by lead 34c, all carried by disc 16. Electrode 30b of the electrolytic cell is extended so as to engage the other side of the battery 32.

Battery 32 also supplies electrical current to a  
35 pair of iontophoresis electrodes 36, 38, to induce the transfer of the drug within compartment 24 via the tubular elements 26 in membrane 10 to the subject's skin. Electrode

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36 is of annular shape and encloses membrane 10 so as to come into contact with the subject's skin when the device 2 is applied to the subject. Electrode 38 is a conductive layer applied to membrane 12 facing the drug compartment 24 so as to come into direct contact with the drug therein.

The drug is introduced into the drug compartment 24 via an injection port 40 received in an opening on one side of the intermediate housing section 4c. A nipple 42 is threadably applied in alignment with an opening in the opposite side of the intermediate housing section 4c and is closed by a hydrophobic filter 44. The liquid drug is introduced into drug compartment 24 via an injection syringe piercing plug 40. Nipple 42 serves as a vent for purging the air from compartment 24 until the vent is closed by contact of the liquid drug with the hydrophobic filter 44 when the compartment is filled with the drug.

Membrane 10 is made of a resilient, deformable material. The tubular elements 26 passing through membrane 10 are preferably made of a stiff, i.e., rigid or semi-rigid, plastic material having an inner diameter of less than 1.0 mm, and projecting at least 0.1 mm from the outer face of membrane 10. As examples, these tubular elements 26 may be made of Teflon (Reg. TM), or of a polycarbonate resin, have an outer diameter of 1.0 mm, an inner diameter of 0.5 mm, and projecting about 0.3 mm from the surface of the drug delivery membrane 10 in contact with the subject's skin. Preferably, they are in the form of hollow metal needles, such as of steel or aluminum coated on their outer surfaces with a coating of insulation, e.g., by oxidation, chemical deposition, etc.

A drug delivery device would usually include at least 50 of such tubular elements, with the outlet ends 26b of each such element firmly engaging the subject's skin so as to effectively seal their inner channels to the subject's skin. These tubular elements thus deliver the drug from compartment 24 directly to a multitude of spaced discrete areas on the subject's skin, and at a rate determined by the

pressure applied to the drug chamber 24 by the displacement of membrane 12.

As one example, membranes 10, 12 and 20 may be of a silicone rubber. Electrically-conductive layer 38 applied to membrane 12, and/or electrode 36 applied to the subject's skin, may also be of a silicone rubber, but with an electrically-conductive filler such as silver, carbon or aluminum particles.

The device illustrated in Figs. 1-3 may be applied to the arm or leg of the subject to receive the drug by the use of the bands 3 such that the inner face of the device, illustrated in Fig. 2, firmly engages the subject's skin. When the device is so applied, the outer ends 26b of the stiff tubular elements 26 passing through the drug-delivery membrane 10 project slightly from the membrane and firmly engage the subject's skin.

Battery 32 supplies electrical current via an electrical switch or other control circuitry (not shown) to both the electrolytic cell electrodes 30a, 30b and to the iontophoresis electrodes 36, 38.

The electrolytic cell 30 generates a gas in accordance with the magnitude of the electrical current applied to its electrolyte 30c. This gas increases the pressure within chamber 28 to displace membrane 12 towards membrane 10, thereby increasing the pressure within the drug chamber 24. Membrane 20, having one side exposed to the pressure within chamber 28 and the other side exposed to the atmosphere, tends to regulate the pressure within chamber 28.

The displacement of membrane 12 towards the drug delivery membrane 10 forces the liquid drug from compartment 24 through the tubular elements 26 in accordance with the pressure in chamber 24. The pressure in chamber 24 also tends to displace membrane 10 outwardly, thereby more firmly pressing the outlet ends 26b of the tubular elements 26 into contact with the subject's skin. It will thus be seen that the rate of feeding of the drug from chamber 24 via tubular



elements 26 to the subject's skin will be controlled by the rate of generation of gas by the electrolytic cell 30.

The transfer of the drug from compartment 24 to the subject's skin is electrically-induced by the voltage applied between the two iontophoresis electrodes 36 and 38. Electrode 36 directly contacts the subject's skin, and electrode 38 directly contacts the drug within compartment 24 delivered to the subject's skin via the tubular elements 26.

It will thus be seen that the delivery of the drug from compartment 24 to the subject's skin is effected in a manner which is both efficient and controllable by controlling the electrical current supplied to the electrolytic cell 30 and also the voltage applied between the two iontophoresis electrodes 36, 38.

Fig. 4 illustrates another device which is generally similar to that of Fig. 3 but includes a number of changes. To facilitate understanding, the elements in the device of Fig. 4 which are generally similar to those in Fig. 3 are correspondingly numbered.

One important difference in the device of Fig. 4 over that of Fig. 3 is that the housing 4 is a two-section housing (rather than a three-section housing), including the two sections 4 and 4b threadedly secured together. The injection port 40 for introducing the drug into the drug reservoir in compartment 24 is located within an opening in housing section 4a.

Another difference in the construction of the device of Fig. 4 over that of Fig. 3 is that the drug delivery body for delivering the drug from the drug compartment 24 is constituted, not by a displaceable membrane 10, but rather by the rigid wall 50 of housing section 4a, which rigid wall carries the stiff tubular elements 26 communicating with the drug compartment 24. Thus, the device of Fig. 4 does not include a membrane corresponding to membrane 10 in Fig. 3.

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The device of Fig. 4, however, does include membranes 12 and 20 defining between them the compartment for the electrolytic cell 30 and battery 32. The latter elements, instead of being received within a socket formed in membrane 12, are rather received within a socket formed in a rigid holder 52 secured between the two housing sections 4a and 4b. The electrolytic cell 30 communicates with chamber 28 between the two membranes 12 and 20, such that the pressure produced in chamber 28 by the gas generated from the electrolytic cell 30, deforms membrane 12 to control the rate of delivery of the drug via the stiff tubular elements 26.

Membrane 20, in the construction of Fig. 4, is secured between housing section 4b and the rigid holder 50 and carries electrical contact 34c on its inner face engageable with electrical contacts 34a and 34b connecting battery 32 to the electrolytic cell 30 to regulate the pressure of the gas within chamber 28. Thus, if an excessive pressure is developed within chamber 28, this will displace the center of membrane 20 outwardly, to cause its contact 34c to disengage from contacts 34a and 34b, thereby de-energizing the electrolytic cell 30 until the excessive pressure within chamber 28 drops to the point where contact 34c again engages contacts 34b and 34a to restart the generation of the gas from the electrolytic cell.

A still further difference in the construction of Fig. 4 over that of Fig. 3 is that in Fig. 4 the iontophoresis electrodes 36 and 38 are omitted. Thus, in the construction of Fig. 4, the delivery of the drug from compartment 24 via the stiff tubular elements 26 is controlled by the rate of generation of gas by electrolytic cell 30. In substantially all other respects, the device of Fig. 4 is constructed, and operates, in substantially the same manner as described above with respect to Fig. 3.

Fig. 5 illustrates another device similar to that of Figs. 3 and 4 but further simplified in construction. To facilitate understanding, those parts which are generally

similar to those in Figs. 3 and 4 are correspondingly numbered.

Thus, the device in Fig. 5 also includes a two-section housing 4a, 4b, as in Fig. 4, with the stiff tubular elements 28 carried by the rigid end wall 50 of housing section 4a. In Fig. 5, however, the drug reservoir compartment 24 is defined by a displaceable membrane 62, generally similar to membrane 20 in Figs. 3 and 4, secured between the two housing sections 4a, 4b, and a partition wall 60 within the housing and formed with a metering orifice 64 for metering the flow of the drug from compartment 24 to the stiff tubular elements 28. Partition 60 is formed with an annular rib 66, or other rib formation, in order to space it from the ends of the stiff tubular elements 28 and to permit the drug to flow thereto from the reservoir in compartment 24 via the metering orifice 64.

Thus, in the construction illustrated in Fig. 5, the control of the rate of delivery of the drug via the stiff tubular elements 28 is effected by the metering orifice 64 of partition 60. Therefore, whenever it is desired to change the drug delivery rate, a partition 60 with the appropriate-size metering orifice 64 would be inserted into the housing 4.

Fig. 6 illustrates another construction, similar to that of Fig. 5, but even further simplified. Those elements in Fig. 6 which generally correspond to those in Fig. 5 are correspondingly numbered to facilitate understanding.

In the construction illustrated in Fig. 6, the partition 60, including its metering orifice 64, is omitted, and instead the rate of delivery of the drug is controlled by the pressure within the drug reservoir chamber 24. The drug is introduced into chamber 24, at the appropriate pressure, via injection port 40, and membrane 62 is displaced outwardly so as to apply a continuous pressure tending to urge the drug to flow from chamber 24 through the stiff tubular elements 28. If the pressure within chamber

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24 drops below that needed for delivering the drug at the desired rate, an additional quantity of the drug may be introduced into compartment 24 via injection port 40.

The outer tips of the stiff tubular elements, 5 therein designated 126, may be cut at a bias, or made conical, to pierce the layer of dead cells on the skin and thereby to enhance the penetration of the drug. Figs. 7a-7e illustrate various configurations of tip constructions. Thus, Fig. 7a illustrates a tip construction 126a of conical 10 configuration; Fig. 7b illustrates the tip 126b having an inwardly-tapered cut; Fig. 7c illustrates the tip 126c as cut at a bias; Fig. 7d illustrates the tip of a flat configuration (similar to that illustrated in Figs. 3-6); and Fig. 7e illustrates the tip 126e as being of frusto- 15 conical configuration.

Where technical features mentioned in any claim are followed by reference signs, those reference signs have been included for the sole purpose of increasing the intelligibility of the claims and accordingly, such reference signs do not have any limiting effect on the scope of each element identified by way of example by such reference signs.

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## CLAIMS:

1. A drug delivery device for delivering a liquid drug to a subject via the subject's skin, comprising:

a housing;

a liquid reservoir in said housing for a liquid drug to be delivered;

and a drug delivery body carried by said housing and having one side communicating with one side of the liquid reservoir, and the opposite side exposed to engage the skin of the subject to receive the drug;

characterized in that said drug delivery body includes a plurality of stiff tubular elements extending through the body, each having an inlet end communicating with said liquid reservoir, and an outlet end at said opposite side of the drug delivery body to conduct the liquid drug directly to said opposite side.

2. The device according to Claim 1, further including control means for controlling the rate of delivery of the drug from said reservoir via said plurality of stiff tubular elements extending through the drug delivery body.

3. The device according to Claim 2, wherein said control means includes a displaceable membrane for controlling the pressure in said reservoir in order to control the rate of feed of the liquid from the reservoir via said tubular elements to the subject's skin.

4. The device according to Claim 3, wherein said drug delivery body is in the form of a second displaceable membrane through which said plurality of stiff tubular elements extend and displaceable by the pressure in said reservoir.

5. The device according to Claim 4, wherein said control means further includes an electrolytic cell capable of generating a gas to displace said first-mentioned membrane corresponding to the electrical current applied to the electrolytic cell.

6. The device according to Claim 2, wherein said control means includes a partition between the liquid

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reservoir and the drug delivery body and formed with a metering orifice for metering the flow of the drug from the reservoir to said drug delivery body.

7. The device according to Claim 1, wherein said housing further includes a first electrode exposed for contact with the skin of a subject, and a second electrode in contact with the liquid drug in said reservoir.

8. The device according to Claim 1, wherein said plurality of stiff tubular elements have inner diameters of less than 1 mm.

9. The device according to Claim 1, wherein said plurality of stiff tubular elements are hollow needles of metal coated externally with insulation.

10. The device according to Claim 1, wherein said drug delivery body includes at least 50 of said stiff tubular elements.

FIG. 1

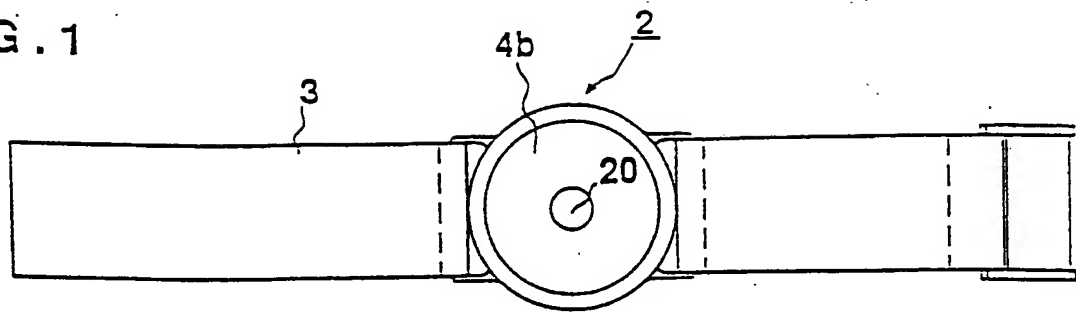


FIG. 2

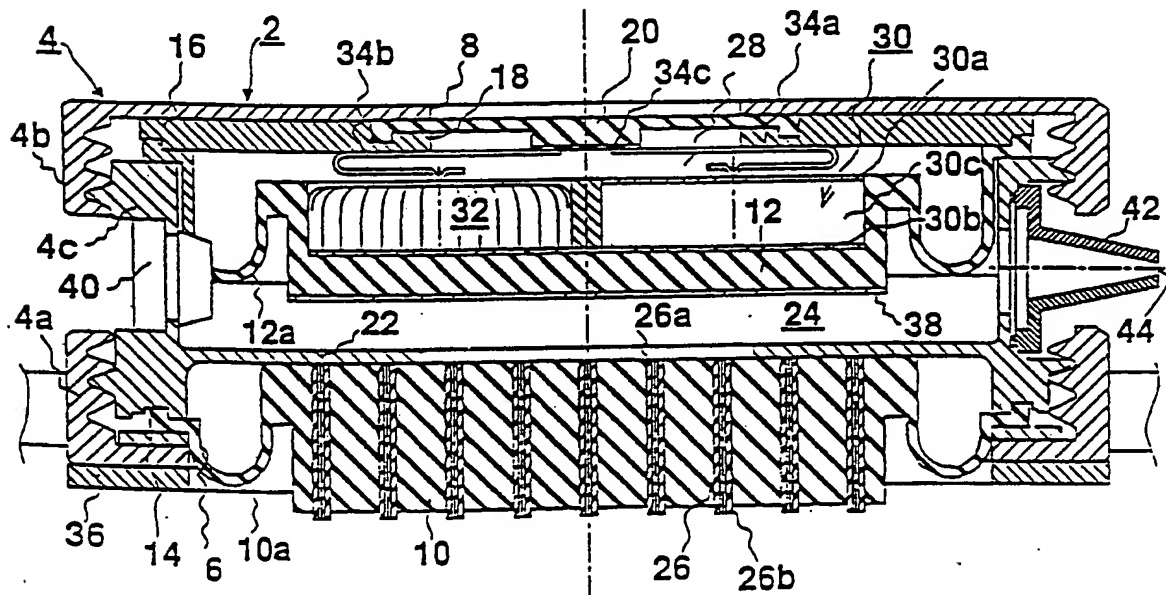
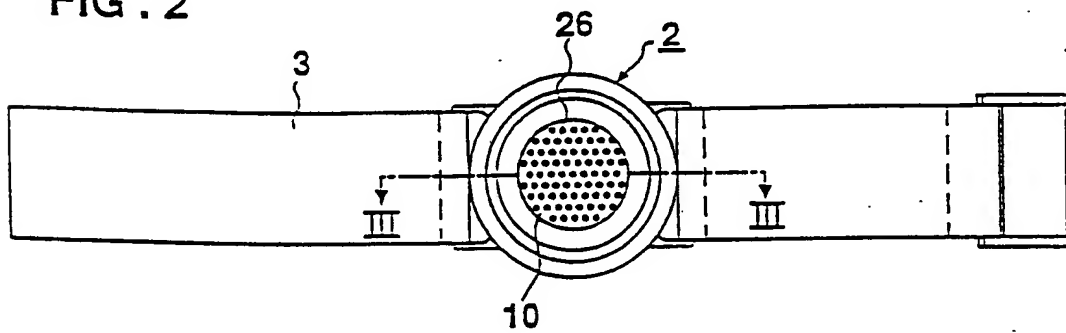


FIG. 3

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FIG. 4

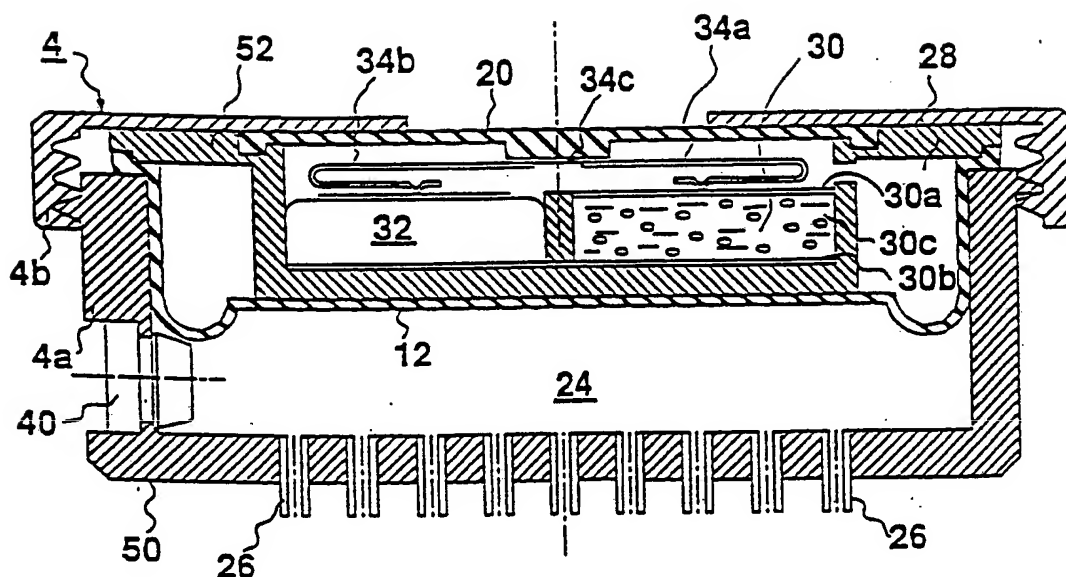
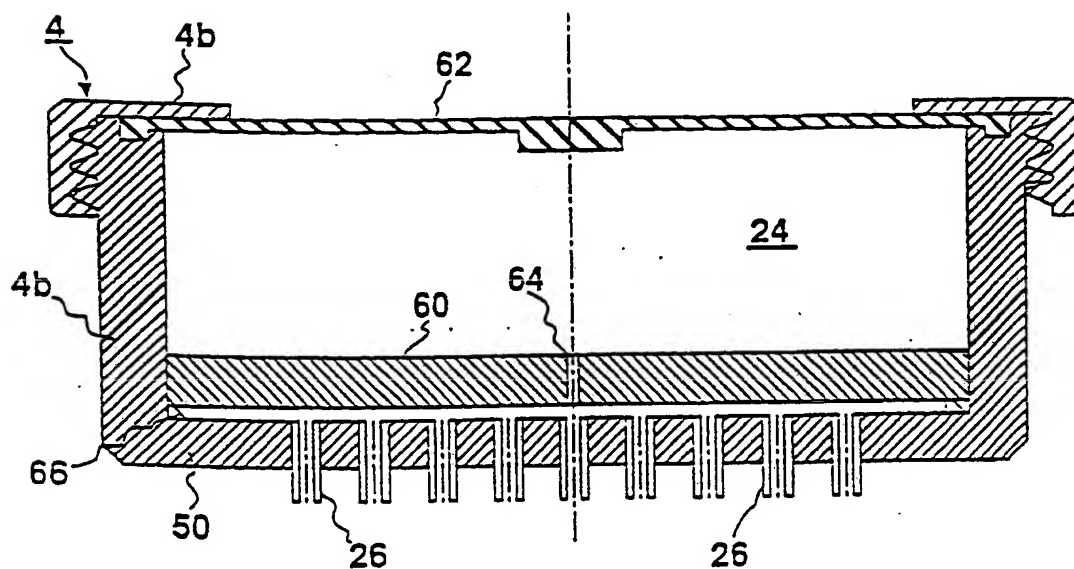


FIG. 5



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FIG. 6

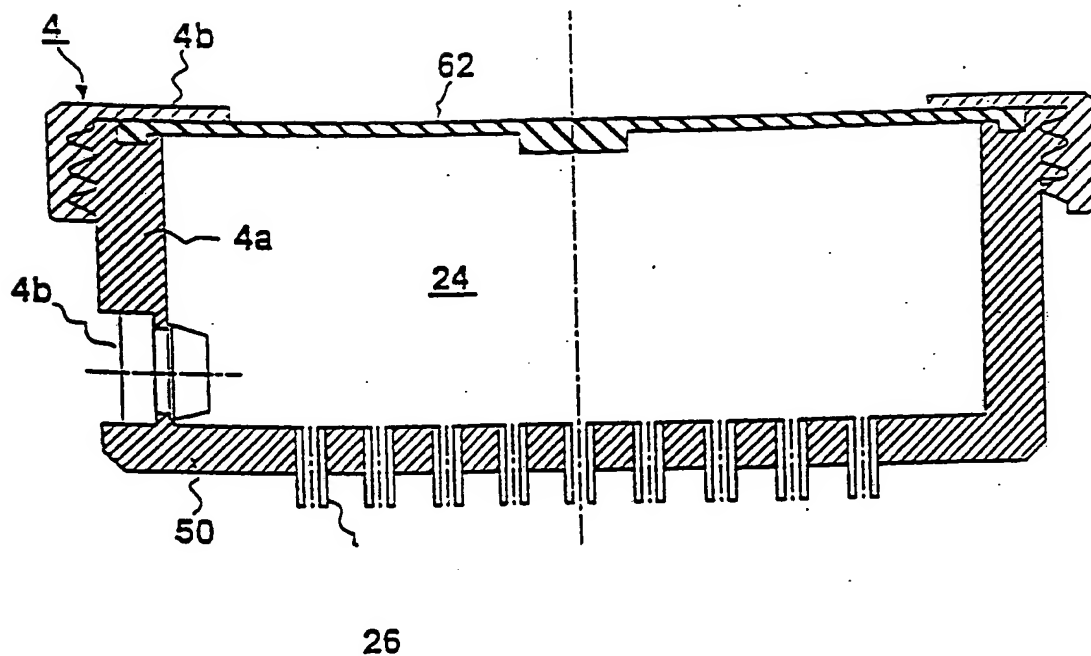


FIG. 7a

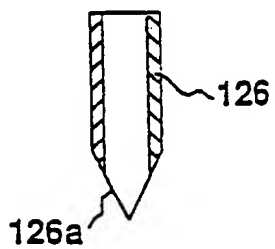


FIG. 7b

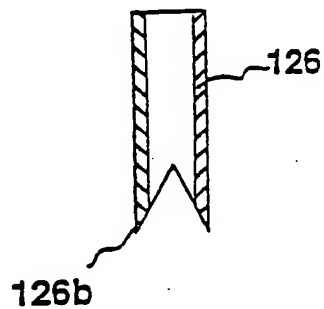


FIG. 7c

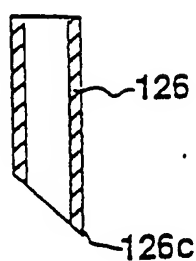


FIG. 7d

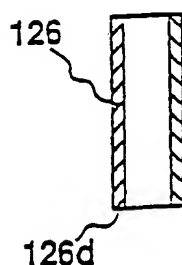
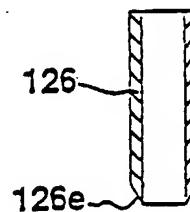


FIG. 7e



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 93/00562

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 A61N1/30		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl. 5	A61N	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	EP,A,0 429 842 (KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY) 5 June 1991 see page 4, line 48 - page 5, line 42; figure 1	1
A	---	2,8,10
A	FR,A,2 562 800 (LABORATOIRES FOURNIER) 18 October 1985 see page 4, line 19 - page 6, line 6; figure 1	1,6,7
A	---	1-3,5,7
A	US,A,5 090 963 (GROSS,ZUCKER) 25 February 1992 cited in the application see column 3, line 13 - column 4, line 59; figures 1-2	
<p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
09 JUNE 1993		09 -07- 1993
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		HERBELET J.C.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

EP 9300562  
SA 71040

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09/06/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0429842	05-06-91	CA-A- 2041250 EP-A- 0509122	23-11-91 21-10-92
FR-A-2562800	18-10-85	None	
US-A-5090963	25-02-92	EP-A- 0481601	22-04-92

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